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(19)

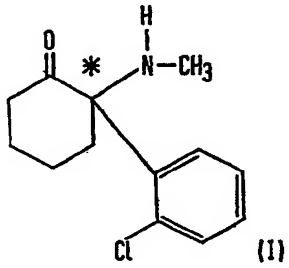
(54) KETAMINE RESOLUTION

(71) We, BRISTOL MYERS COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, of 345 Park Avenue, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for resolving racemic 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone, optical isomers thereof and nontoxic pharmaceutically acceptable salts thereof.

The invention is predicated on the discovery that racemic 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone (Ketamine) may be resolved using tartaric acid to produce an optical isomer which as the base is levorotatory in ethanol and as the hydrochloride salt is dextrorotatory in water. This isomer was found to have improved anaesthetic and anticonvulsant activity in various species of animals, including man.

Racemic 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone (ketamine) and its hydrochloride salt and relatives have been described in United States Patent No. 3,254,124 and ketamine has the formula:



(I)

* denotes asymmetric carbon atom

The central nervous system activities of ketamine hydrochloride and in particular its anaesthetic activity in various animal species has been described [D. A. McCarthy, G. Chen, D. H. Kaump, and C. Ensor, *J. New Drugs*, 5, 21 (1965)]. Good analgesic and anaesthetic activity has been confirmed in initial clinical studies: [E. F. Domino, P. Chodoff and G. Corssen, *Clin. Pharmacol. Ther.*, 6, 279 (1965)]. The principal disadvantage of ketamine hydrochloride as an injectable anaesthetic is its occasional adverse psychic effect; thus during emergence from anaesthesia the patient may go through a phase of vivid dreaming with or without psychomotor activity, manifested by confusion and irrational behaviour.

A resolution of ketamine has not been described previously. In general while optical isomers have the same physical-chemical properties (except for their rotation of plane polarized light), their biological activities could be expected to be different. However, with a multi-active racemate one cannot predict the biological activity associated with each optical isomer. The activities can only be assigned through resolution and biological testing.

It was hoped that resolution of ketamine would result in a product with less side effects and/or a greater therapeutic index.

In accordance with this invention there is provided a process for resolving racemic 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone having the above formula (I), which process comprises adding an enantiomorph of tartaric acid to a solution of said racemic 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone to form the tartaric acid salt of 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone and subsequently isolating an isomer of 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone.

In one aspect the process of the invention may be carried out by adding (+)-tartaric acid to a solution of said racemic 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone to form the (+)-tartaric acid salt of (−)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone and the optical isomer (−)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone which is levorotatory in ethanol may be recovered by treating the salt with a strong alkaline material e.g. sodium hydroxide. If desired hydrochloric acid may be added to the (−)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone to form the hydrochloride salt which is dextrorotatory in water.

The (+)-tartaric acid salt of (−)-2-chlorophenyl)-2-methylaminocyclohexanone may initially be formed in acetone-water, washed in acetone and then subjected to recrystallization from acetonitrile prior to isolation of the optical isomer. In this case the mother liquors resulting from the acetone wash and recrystallization may be treated with a strong alkaline material e.g. sodium hydroxide, to yield a partially resolved mixture of bases enriched in (+)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone. Tartaric acid may then be added to the partially resolved mixture to form the (−)-tartaric acid salt of (+)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone, which, upon decomposition yields (+)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone which is dextrorotatory in ethanol. Again, if desired, hydrochloric acid may be added to the (+)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone to form the hydrochloride salt which is levorotatory in water and ethanol.

The invention also provides optical isomers of 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone.

Preferred embodiments of the present invention are solid, substantially pure 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone having a negative $[\alpha]_D^{25}$ of greater than 50° at a concentration of 2.00 grams/100 cc. in ethanol and solid, substantially pure 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone hydrochloride having a positive $[\alpha]_D^{25}$ of greater than 91° at a concentration of 2.00 grams/100 cc. in water.

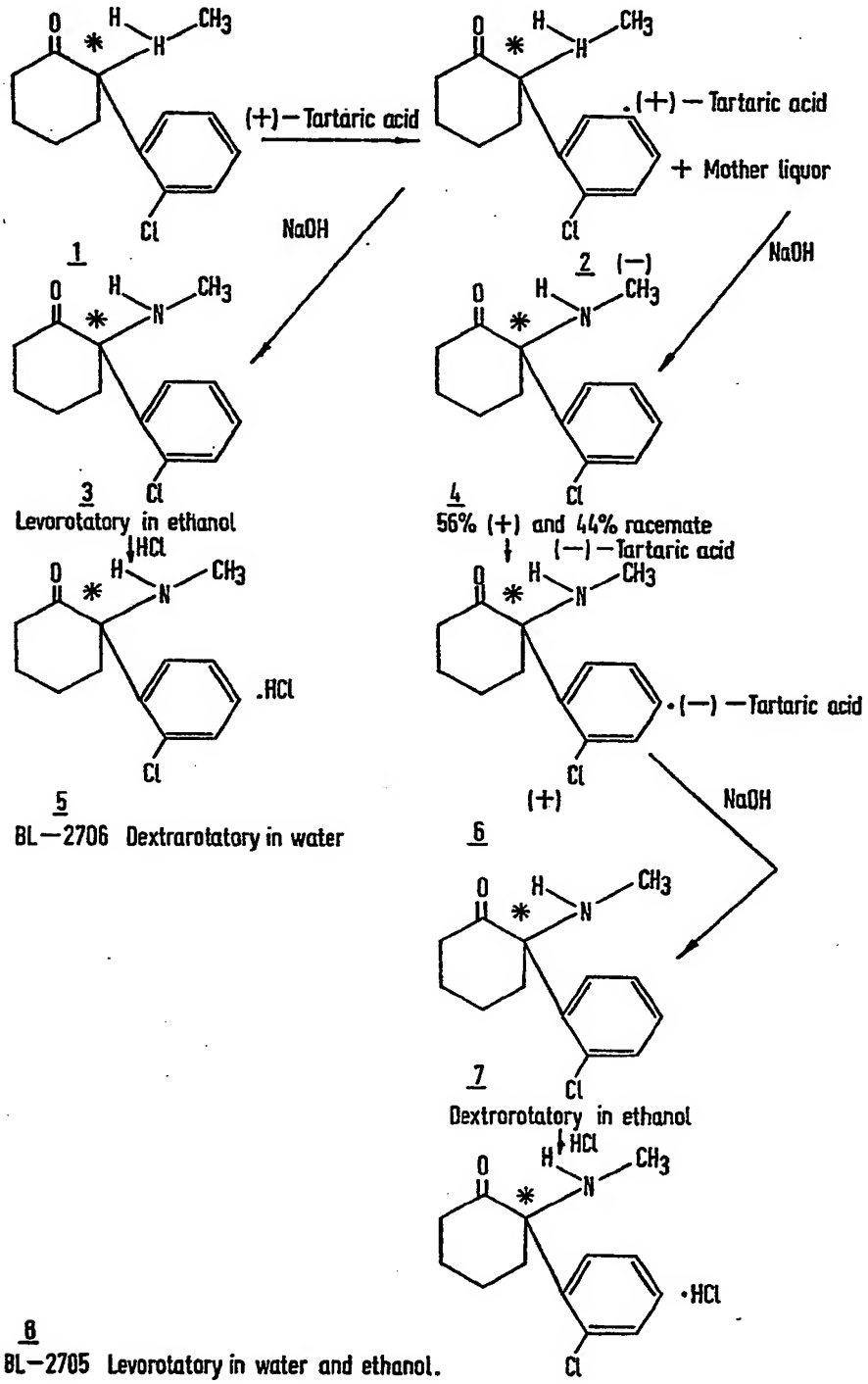
The pharmaceutically acceptable nontoxic salts include the organic and inorganic acid addition salts, e.g., those prepared from acids such as hydrochloric, sulfuric, sulfamic, tartaric, fumaric, hydrobromic, glycolic, citric, maleic, phosphoric, succinic, acetic and nitric acid.

The compounds of the present invention, and particularly the very water-soluble hydrochloride are used in animals, and especially in man, as aqueous solutions which contain, for example, the equivalent of 5, 10 or 50 mgm. of free base per ml. Such solutions may also contain a preservative, e.g. they may contain 1:10,000 benzethonium chloride, they may be made isotonic with sodium chloride and they may be adjusted if necessary to a slightly acidic pH, e.g., 3.5 to 5.5.

For induction of surgical anaesthesia for a brief period of time such as 5 to 25 minutes use is made of an intravenous dose of about 1 to 2 mgm./kg. or an intramuscular dose of about 5 to 15 mgm./kg. If a longer effect is desired, including periods of six hours or longer, additional increments can be administered to maintain anaesthesia.

Thus, the invention includes a pharmaceutical composition, which composition comprises a 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone in accordance with the invention or a nontoxic pharmaceutically acceptable acid addition salt thereof and a carrier.

The following reaction scheme illustrates the resolution of ketamine by the process of the invention:



Treatment of ketamine (*1*) with (+)-tartaric acid gave the (+)-tartaric acid salt of (−)-2-(o-chlorophenyl)-2-methylaminocyclohexanone (*2*). Decomposition of this diastereoisomeric salt (*2*) with sodium hydroxide gave the free base (*3*) which was converted to its hydrochloride salt, BL—2706, (*5*) for testing.

In a similar manner BL—2705 (*8*) was isolated from mother liquors through diastereoisomeric salt formation with (−)-tartaric acid. Alternatively, treatment of ketamine with (−)-tartaric acid could be expected to lead to preferential crystallization of the (−)-tartaric acid salt of (+)-2-(o-chlorophenyl)-2-methylaminocyclohexanone (*6*).

Upon conversion to their respective hydrochlorides the sign of rotation of the free bases *3* and *7* change. Therefore the prefixes (+) and (−) should only be used with the full name to avoid confusion.

Preliminary pharmacologic data indicate that BL—2706 is the more potent optical isomer in several tests using different animal species. This makes the process especially attractive in that the more potent isomer can be isolated using a readily available resolving agent (natural tartaric acid) which is itself a nontoxic, pharmaceutically acceptable substance. Therefore in essentially a one-step process the more potent isomer of ketamine can be isolated in acceptable form.

The ease with which resolution of ketamine could be achieved was a surprising discovery which followed unsuccessful attempts at that resolution using each of the following resolving agents:

1. 1-α-bromocamphor-π-sulfonic acid,
2. d-camphoric acid,
3. d-10-camphorsulfonic acid,
4. (+)-5-cyclohexyl-1-indancarboxylic acid,
5. l-mandelic acid,
6. l-malic acid,
7. l-2-pyrrolidone-5-carboxylic acid,
8. l-quinic acid,
9. (2R:3R)-2′-bromotartranilic acid,
10. (2R:3R)-4′-bromotartranilic acid monohydrate,
11. (2R:3R)-2′-chlorotartranilic acid,
12. (2R:3R)-2′-nitrotartranilic acid,
13. (2R:3R)-2′,4′,6′-tribromotartranilic acid, and
14. (2R:3R)-2′,4′,6′-trichlorotartranilic acid.

Following is a description by way of example of the resolution of ketamine in accordance with the invention. Melting points are uncorrected and temperatures are expressed in degrees Centigrade (°C).

Example 1.

(+)-Tartaric Acid Salt of (−)-2-(*o*-Chlorophenyl)-2-methylaminocyclohexanone (2)

(+)-Tartaric acid (10.3 g., 0.0686 mole) was added to a solution of racemic 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone (16.3 g., 0.0686 mole) in acetone (200 ml.). The mixture was heated to boiling and then clarified at the boiling point by the addition of water (13 ml.). The hot solution was partially cooled and was then seeded with the (+)-tartaric acid salt of (−)-2-(o-chlorophenyl)-2-methylaminocyclohexanone. [The seed crystals were obtained from a small scale experiment]. The mixture was allowed to cool slowly and then stand at 25° for 17.5 hours. The colorless needles were collected and washed with cold acetone to give a mixture of salts (19.68 g.), m.p. 89—95°. Two recrystallizations from acetonitrile gave the (+)-tartaric acid salt of (−)-2-(o-chlorophenyl)-2-methylaminocyclohexanone (10.4 g.), m.p. 140—142°.

The acetone-water and first acetonitrile mother liquors were retained for eventual isolation of (+)-2-(o-chlorophenyl)-2-methylaminocyclohexanone.

Example 2.

(−)-2-(o-Chlorophenyl)-2-methylaminocyclohexanone (3).

The (+)-tartaric acid salt of (−)-2-(o-chlorophenyl)-2-methylaminocyclohexanone (10.4 g.) was partitioned between diethyl ether (150 ml.) and 0.5 *N* sodium hydroxide (120 ml.). The ethereal layer was washed with water (60 ml.), followed by water saturated with sodium chloride (60 ml.) and dried (sodium sulfate). The ethereal solution was reducde to dryness to leave (−)-2-(o-chlorophenyl)-2-methylaminocyclohexanone (6.15 g.): m.p. 109—118.5° with prior shrinking; $[\alpha]_D^{25} - 50.30°$ (*c* 2.00, ethanol). Recrystallization from cyclohexane gave long colorless needles (5.16 g.): m.p. 120—122°; $[\alpha]_D^{25} - 56.35°$ (*c* 2.00, ethanol).

Example 3.

(+)-2-(o-Chlorophenyl)-2-methylaminocyclohexanone Hydrochloride BL—2706 (5).

Hydrochloric acid (21.0 ml. of 1.0 *N*, 0.021 mole) was added to a mixture of (−)-2-(o-chlorophenyl)-2-methylaminocyclohexanone (4.93 g., 0.0208 mole) and water (21 ml.). The mixture was heated on a steam bath (2 minutes) to nearly complete solution. Ethanol (40 ml.) was added to the warm mixture and the resulting solution was reduced to dryness to leave colorless crystals (+)-2-(o-chlorophenyl)-2-methylaminocyclohexanone hydrochloride: m.p. 265—266.5° (dec); $[\alpha]_D^{25}$ +91.88° (*c* 2.00, water). Recrystallization from ethanol gave colorless needles (4.15 g.): m.p. 259—261° (dec); $[\alpha]_D^{25}$ +92.48° (*c* 2.00, water).

Anal. Calcd. for $C_{13}H_{16}ClNO.HCl$: C, 56.95; H, 6.25; Cl, 25.86; N, 5.11
Found: C, 56.70; H, 6.47; Cl, 26.00; N, 5.10.

Example 4.

(−)-Tartaric Acid Salt of (+)-2-(o-Chlorophenyl)-2-methylaminocyclohexanone (6).

The acetone-water and first acetonitrile mother liquors from Example 1 were combined and reduced to dryness to leave a colorless froth (15.6 g.). The froth was partitioned between diethyl ether (250 ml.) and 0.5 *N* sodium hydroxide (200 ml.). The ethereal layer was washed with water (100 ml.), followed by water saturated with sodium chloride (100 ml.). The ethereal solution was dried (sodium sulfate), filtered and the filtrate reduced to dryness to leave a partially resolved mixture of bases (8.7 g.), m.p. 91—117°, enriched in (+)-2-(o-chlorophenyl)-2-methylaminocyclohexanone, $[\alpha]_D^{25}$ +31.88° (*c* 2.00, ethanol).

(−)-Tartaric acid (5.5 g., 0.0367 mole) was added to a solution of this partially resolved mixture (8.7 g., 0.0367 mole) in acetone (100 mole.). The mixture was heated to boiling and then clarified at the boiling point by the addition of water (65 ml.). The solution was allowed to cool slowly and then stored at 25° for 21 hours. The colorless crystals were collected, washed with cold acetone and dried to give the (−)-tartaric acid salt of (+)-2-(o-chlorophenyl)-2-methylaminocyclohexanone (12.43 g.), m.p. 143—148° with partial melting at 96°. Recrystallization from acetonitrile gave colorless crystals (10.06 g.), m.p. 144—148°.

Example 5.

(+)-2-(o-Chlorophenyl)-2-methylaminocyclohexanone (7).

In a similar manner to Example 2 the (−)-tartaric acid salt of (+)-2-(o-chlorophenyl)-2-methylaminocyclohexanone (10.06 g., m.p. 144—148°) was decomposed with aqueous sodium hydroxide and the free base extracted into ether. Removal of the ether gave (+)-2-(o-chlorophenyl)-2-methylaminocyclohexanone (5.82 g.): m.p. 119—122°; $[\alpha]_D^{25}$ +56.5° (*c* 2.00, ethanol). Recrystallization from cyclohexane gave long colorless needles (5.42 g.): m.p. 120—122°; $[\alpha]_D^{25}$ +56.78° (*c* 2.00, ethanol).

Example 6.

(−)-2-(o-Chlorophenyl)-2-methylaminocyclohexanone Hydrochloride. BL—2705 (8).

In a similar manner to Example 3 (+)-2-(o-chlorophenyl)-2-methylaminocyclohexanone (5.21 g.) was treated with an equivalent of aqueous hydrochloric acid to give (−)-2-(o-chlorophenyl)-2-methylaminocyclohexanone hydrochloride: m.p. 265—266° (dec); $[\alpha]_D^{25}$ − 92.18° (*c* 2.00, water). Recrystallization from ethanol gave colorless needles (4.43 g.): m.p. 259—261° (dec); $[\alpha]_D^{25}$ − 91.88° (*c* 2.00, water).

Anal. Calcd for $C_{13}H_{16}ClNO.HCl$: C, 56.95; H, 6.25; Cl, 25.86; N, 5.11.
Found: C, 56.80; H, 6.35; Cl, 25.60; N, 5.17.

Pharmacology

Some detailed pharmacological comparisons of the racemate of 2-(*o*-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride (ketamine), its dextrorotatory isomer (BL—2706) and its levorotatory isomer (BL—2705), particularly with respect to anaesthetic and anticonvulsant activities, were carried out in several animal species and the details of these comparisons are given below.

The main objective of the study was to determine whether there was any separation of the activities observed with ketamine between the two optical isomers.

Materials

All doses refer to the hydrochloride salt and not the free base. Bl—2705 and 2706 were supplied as the solid HCl and solutions were prepared in saline immediately

before use. All three compounds were freely soluble in water. For convenience in the tables below, the hydrochloride which is dextrorotatory in water is referred to as BL—2706 and the less potent levorotatory (in water) isomer of ketamine hydrochloride is referred to as BL—2705.

The acute toxicities of the three compounds were determined in mice using various routes of administration. The LD_{50}'s were determined using Weil's method and groups of four animals. Results are summarised in Table 1.

TABLE 1

Route	LD_{50}, mg./kg. Ketamine HCl	BL-2705	BL-2706
Oral	539	625	559
Intraperitoneal	213	263	236
Intravenous	68	68	54

These toxicities are not considered to be significantly different because of the small number of animals used.

Anti-Convulsant Studies

Two studies were done in mice. In the first the ED_{50} for each drug for protection against tonic extensor convulsions induced by maximal electroshock was determined. The electroshock was of 8 mA and 0.5 sec. duration and was applied through corneal electrodes. The animals were shocked 5 minutes after intravenous dosing. Ten animals were used per group and ED_{50}'s were determined by log-probit plot. The ED_{50}'s for the three compounds with their standard errors were as follows: ketamine HCl, 2.85±0.37 mg./kg.; BL—2705, 4.6±0.74 mg./kg.; BL—2706, 2.25±0.43 mg./kg.

In the second study the current required to produce tonic extension of the hind limbs of 50% of animals pretreated with varying intravenous doses of the three compounds was determined. The electroshock was of 0.5 sec. duration and was delivered as described above. Groups of 10 mice were used and they were dosed intravenously 5 minutes before shock. Tonic current 50 was determined by log-probit plot. The results of this study are summarized in Table 2. Diphenylhydantoin sodium was included in this study to show that the curves obtained with ketamine were typical of anticonvulsants. The diphenylhydantoin was administered intraperitoneally 30 minutes before shock. It was seen that with ketamine HCl and BL—2706 there is a critical dose above which the anticonvulsant properties of the compounds increase dramatically; this was also seen with diphenylhydantoin. BL—2705, however, did not demonstrate this dramatic inflection and doses higher than 20 mg./kg. iv could not be used as toxicity was encountered. The 5 minute predose was found to be critical as anticonvulsant potency was found to decrease if the animals were left longer.

TABLE 2

The Current (mA) Required to Produce 50% Tonic Extension after Various Drugs and Doses

Drug/Dose mg/kg	0	5	7.5	10	15	20	30
Ketamine HCl iv	6.4±.29	9.3±.72	—	34.4±4.8	106±14	—	—
BL-2705 iv	6.4±.29	8.0±.52	—	12.6±1.4	—	19.4±4.7	—
BL-2706 iv	6.4±.29	10.8±.59	12.5±1.8	116±15	—	—	—
Diphenylhydantoin ip	6.4±.29	7.0±.45	—	7.2±.54	—	26.0±4.3	150±27

Hypnotic Action in Rats

The intraperitoneal dose of all three compounds producing loss of righting reflex in 50% of rats was determined. The righting reflex was considered lost if a rat would stay on its back for more than 10 sec. The intraperitoneal HD_{50} values were as follows: ketamine HCl, 50.4 mg./kg.; BL—2705, 76.1 mg./kg.; BL—2706, < 40 mg./kg. (inadequate supply). In contrast to larger laboratory animals all three compounds produced a general behavioural profile in rats more like that seen with the clsasical anesthetics in that the animals were very relaxed with little muscle tone.

Anesthetic Action in Cats

Three studies were carried out. In the first a three cat cross-over on successive days was performed using a dose of 10 mg./kg. im of each drug. Three times were recorded: the time from injection to loss of the righting reflex (induction); the time from loss to return of the righting reflex (anesthesia); the time from return of the righting reflex until the animal stood on all four feet (recovery). The results of this experiment are given in Table 3.

TABLE 3

Three Cat cross-over study using a dose of 10mg./kg. im. Times of the various stages are recorded in minutes

Ketamine HCl

Cat No.	Induct.	Anesth.	Recovery
472	3	50	8
476	9	24	36
481	2	32	10
Mean	5	35	18

BL-2705

Cat No.	Induct.	Anesth.	Recovery
472	7	10	5
476	0*	0	0
481	0**	0	14
Mean	2	3	6

BL-2706

Cat No.	Induct.	Anesth.	Recovery
472	5	37	15
476	4	29	40
481	4	32	10
Mean	4	33	22

* When this cat received BL-2705 it exhibited extreme ataxia for 45 minutes but remained standing.

** This cat could not stand after receiving BL-2705 but was never anesthetic.

In a second study which was not of cross-over design each drug was given to four cats at a dose of 10 mg/kg. iv into the cephalic vein. In this experiment induction was immediate and only two stages were recorded: time from injection to return of the righting reflex (anathesia); time from return of the righting reflex until the animal stood on all four feet (recovery). The results of this experiment are summarized in Table 4.

TABLE 4

Study of Ketamine and Isomers in Cats at 10 mg./kg. iv. Times are Recorded in Minutes

	Ketamine HCl		BL-2705		BL-2706	
Experiment	Anesth.	Recovery	Anesth.	Recovery	Anesth.	Recovery
1	25	15	12	4	26	15
2	12	13	10	7	15	14
3	26	21	9	10	15	6
4	6	17	8	13	20	27
Mean	17	16	10	8	19	15

In the third study 6 cats, 3 male and 3 female, were used in a cross-over design and 4 days were allowed between doses. A dose of 20 mg./kg. iv of each compound was used. Three stages were recorded: time from injection until the head was lifted from the floor (anesthesia 1); time from head lift until the cat lifted its shoulders (anesthesia 2); time from shoulder lift until the cat stood on all 4 legs (recovery). The results of this study are given in Table 5.

TABLE 5

Cross-Over Study of Ketamine and Isomers in Cats at 20 mg./kg. iv. Times are Recorded in Minutes

	Ketamine HCl		
Cat No.	Anesth. 1	Anesth. 2	Recovery
471	20	26	26
472	30	42	37
476	14	14	20
481	26	50	36
479	37	69	6
482	32*	52	16
Mean	26	42	23

TABLE 5 (continued)

BL-2705

Cat No.	Anesth. 1	Anesth. 2	Recovery
471	0	10	18
472	0	10	23
476	4	9	18
481	0	0	15
479	11	21	10
482	15	18	4
Mean	5	11	15

BL-2706

Cat No.	Anesth. 1	Anesth. 2	Recovery
471	32	40	25
472	40	45	45
476	29	34	55
481	37	69	8
479	50	58	56
482	32	45	43
Mean	37	48	39

* Cat No. 482 had respiratory arrest when given ketamine and was artificially ventilated for 2 minutes.

Salivation seen in all cats and the degree seemed to correlate well with the duration of anesthesia. Considerable muscle tone was always seen and this was most marked in the front legs; the cats had a simliar posture to that seen after decerebration. Analgesia was only observed when anesthesia occurred. All reflexes tested were present throughout with the exception of pupil constriction to strong light, extreme mydriasis was always seen.

Anesthetic Action in Monkeys

The action of the three compounds was studied in squirrel monkeys (Saimiri sciureus). Monkeys were considered anesthetic when they could be placed on their sides. The recovery stage was taken as the time from the animal rolling over onto its chest until it either stood or moved into a crouching position.

At a dose of 10 mg./kg. im none of the compounds produced anesthesia (loss of the righting reflex). The monkeys receiving ketamine or BL-2706 became extremely ataxic and those receiving BL-2705 slightly ataxic.

At a dose of 20 mg./kg. im in four monkeys, BL-2705 produced no anesthesia but considerable ataxia was seen in all cases. The effects of ketamine and BL-2706 at a dose of 20 mg./kg. im in an 8 monkey cross-over study are given in Table 6.

TABLE 6

Ketamine and BL-2706, 20 mg./kg. im. in Monkeys

Ketamine HCl

Monkey No.	Induction	Anesthesia	Recovery
25	2.5	17.5	7.5
26	3	14	10.5
40	2.5	27.5	1.5
44	2	6	2
51	3.5	26	1
39	7.5	4	4.5
45	5.5	4.5	11
48	3	6.5	2.5
Mean	3.5	13	5

BL-2706

Monkey No.	Induction	Anesthesia	Recovery
25	4	28	2.5
26	3.5	24.5	3.5
40	2.5	39.5	2
44	1.5	8.5	16.5
51	2.5	25.5	2.5
39	3	14	7
45	4.5	14	6.5
48	1.5	14	7.5
Mean	3	21	6

The difference between the mean durations of anesthesia with BL-2706 and ketamine was significant at $p = 0.1$.

Salivation was observed in some monkeys receiving ketamine of BL-2706 at a dose of 20 mg./kg. im.

The anesthetic potential of ketamine is difficult to evaluate in laboratory animals as it does not produce the classical picture seen with general anesthetics. However, in all our tests BL-2705 was less active than ketamine and BL-2706 tended to be more active than the racemate.

The data from the cat and monkey studies suggest that BL-2706 may provide a more consistent response than ketamine. In none of our studies was analgesia observed without anesthesia. All thee compounds gave extremely smooth induction of anesthesia after either intravenous or intramuscular administration.

A dose of 10 mg./kg. of ketamine or BL-2706 in cats appeared to be more active after intramuscular than intravenous administration. No reason can be offered for this

phenomenon other than that after intravenous administration the drug will be more quickly exposed to the liver and kidney for metabolism or excretion.

The recovery phase from anesthesia was similar with all the compounds and there was no significant differences in its relative duration.

One of the main problems with ketamine in man is an incidence of hallucinations during recovery and there is no way of detecting this in laboratory animals. However, one could hypothesize that this might be due to the less active isomer of ketamine (BL-2705) having an imperfect fit on receptors in the CNS which could lead to disorders of mental function. This can only be tested in man.

It is concluded that there is no separation of qualitative activity between the optical isomers of ketamine but there is a potency separation. The dextrorotatory isomer (BL-2706) is considerably more potent than the levorotatory isomer (BL-2705) and somewhat more potent than the racemic mixture in animals as described above. BL-2706 may provide a cleaner and more predictable anesthesia than ketamine in man.

WHAT WE CLAIM IS:—

1. An optical isomer of 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone.

2. A compound as claimed in claim 1 which in the form of the free base is levorotatory in ethanol.

3. A nontoxic, pharmaceutically acceptable acid addition salt of a compound as claimed in claim 1 which is dextrorotatory in water.

4. A compound as claimed in claim 1 which is solid, substantially pure 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone having a negative $[\alpha]_D^{25}$ of greater than 50° at a concentration of 2.00 grams/100 cc. in ethanol.

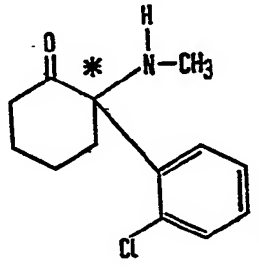
5. The hydrochloride salt of the compound claimed in claim 4.

6. A compound as claimed in claim 1 which is solid, substantially pure 2-(*o*-chlorophenyl)-2-methylaminocyclo hexanone hydrochloride having a positive $[\alpha]_D^{25}$ of greater than 91° at a concentration of 2.0 grams/100 cc. in water.

7. A compound as claimed in claim 1 which in the form of the free base is dextrorotatory in ethanol.

8. A nontoxic, pharmaceutically acceptable acid addition salt of a compound as claimed in claim 1 which is levorotatory in water.

9. A process for resolving racemic 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone having the formula



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which process comprises adding to enantiomorph of tartaric acid to a solution of said racemic 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone to form the tartaric acid salt of 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone and subsequently isolating an isomer of 2-(*o*-chlorophenyl-2-methylaminocyclohexanone.

10. A process as claimed in claim 9, wherein (+)-tartaric acid is added to a solution of said racemic 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone to form the (+)-tartaric acid salt of (—)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone, and the optical isomer (—)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone which is levorotatory in ethanol is recovered from said salt by treating the salt with a strong alkaline material.

11. A process as claimed in claim 10, wherein the strong alkaline material is sodium hydroxide.

12. A process as claimed in claim 10 or claim 11, wherein the (+)-tartaric acid salt of (—)-2-*o*-chlorophenyl)-2-methylaminocyclohexanone is initially formed in acetone-water, washed in acetone and then subjected to recrystallization from acetonitrile prior to isolation of the optical isomer.

13. A process as claimed in any one of claims 10 to 12, wherein hydrochloric acid is added to the (−)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone to form the hydrochloride salt which is dextrorotatory in water.

14. A process as claimed in claim 12, wherein the mother liquors resulting from the acetone wash and recrystallization are treated with a strong alkaline material to yield a partially resolved mixture of bases enriched in (+)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone.

15. A process as claimed in claim 14, wherein teh strong alkaline material is sodium hydroxide.

16. A process as claimed in claim 14 or claim 15, wherein (−)-tartaric acid is added to the partially resolved mixture to form the (−)-tartaric acids salt of (+)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone, which, upon decomposition yields (+)-2-(*o*-chlorophenyl)-2-methylamino-cyclohexanone which is dextrorotatory in ethanol.

17. A process as claimed in claim 16, wherein hydrochloric acid is added to the (+)-2-(*o*-chlorophenyl)-2-methylaminocyclohexanone to form the hydrochloride salt which is levorotatory in water and ethanol.

18. A process as claimed in claim 9 substantially as hereinbefore described in the specific Examples.

19. An optically active isomer of 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone or a nontoxic, pharmaceutically acceptable acid addition salt thereof when isolated by a process as claimed in any one of claims 9 to 18.

20. A pharmaceutical composition, which composition comprises a 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone as claimed in any one of claims 1, 2, 4, 7 or 19 or a salt thereof as claimed in any one of claims 3, 5, 6, 8 or 19 and a carrier.

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